The Spectrum Produced by Malignant Carcinoid Tumor

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. ANTHONY SEBASTIAN*: The patient, a 35-year-old Caucasian mother of two, entered Herbert C. Moffitt Hospital with chief complaint of severe flushing episodes. The present illness began 13 months ago with the first of recurring episodes of diarrhea and flushing of the face. These episodes increased in severity. Two months after onset they were accompanied by severe, constant epigastric pain, and after another two months by severe crushing substernal chest pain. Eight months before admission, the patient became anorectic and began to lose weight. She was admitted to the San Francisco General Hospital where the diagnosis of a malignant carcinoid tumor was made.

On liver scan, she was found to have metastatic disease to the left lobe of the liver. Laboratory studies showed elevation of urinary 5-hydroxyindolacetic acid and of plasma serotonin. A provocative test with intravenous injection of epinephrine precipitated a severe flushing episode. Left lobar hepatectomy was carried out and an extensive search of the bowel at this time failed to reveal a primary source. Microscopic examination of the liver confirmed the diagnosis. Postoperatively, the patient had an acute transitory episode of acute psychosis. Thereafter, she did quite well and for several months was completely free of symptoms until two months ago when anorexia and flushing episodes recurred.

On physical examination, the patient was noted to be thin and apprehensive. Vital signs were normal except for intermittent tachycardia. The skin was clear, without telangiectasia. No abnormality was heard on auscultation of the lungs. There was a grade III systolic ejection murmur, best heard in the third intercostal space along the left sternal border, associated with an ejection click. The liver was enlarged below the level of the umbilicus and was smooth and slightly tender. The spleen was felt 3 cm below the left costal margin. The rest of the physical examination was within normal limits.

Laboratory data included increased serum alkaline phosphatase, depressed prothrombin time, slightly elevated butanol-extractable iodine, and elevated urinary 5-hydroxyindolacetic acid both before and after flushing attacks. During her stay in hospital the patient had several episodes of flushing, lasting as long as 45 minutes, accompanied by apprehension, tremulousness, hyperventilation, intense erythema of the face, arms, chest and neck, tachycardia, slightly decreased blood pressure and pronounced conjunctival injection. She complained of severe abdominal cramping pain, nausea and stabbing pain in the chest. An electrocardiogram taken during one of the episodes was normal, and in none of them were diaphoresis, dyspnea, wheezing, facial edema, lacrimation or pupillary changes observed.

DR. WARREN M. RUSSELL*[1]: A roentgenogram of the chest showed that a thoracotomy had been performed and there was some regrowth of bone along the rib tract. The right diaphragm was con-

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siderably elevated and the liver was large. A gastrointestinal series demonstrated displacement of the stomach to the right and anteriorly by a very large mass in the region of the liver, presumably a greatly enlarged liver. A late film, with most of the contrast medium in the colon, demonstrated a large liver and abnormally large bowel. Much of the colon, particularly the transverse portion, was moderately dilated with some areas of extrinsic indentation. On fluoroscopic examination the transverse colon appeared relatively fixed. Many portions of the large and small bowel had edematous folds suggesting vascular or lymphatic obstruction, although a similar appearance has been seen in the carcinoid syndrome, without metastatic lesions. The terminal ileum was only faintly visualized but it also appeared edematous. The overall appearance was nonspecific; it would be consistent with a diffuse peritoneal carcinomatosis from any source.

DR. KENNETH L. MELMON*[2]: This disease is a fascinating one which has stimulated a great deal of research in the 10 to 12 years since its recognition. The syndrome was initially described by Thorson and Waldenstrom.[1] Dr. Waldenstrom is a very astute clinician. Several years ago he had a young patient who had relatively few symptoms but complained of flushes. On examination the murmur of pulmonic stenosis was heard. Dr. Waldenstrom was unable to explain any relationship between the flushes and the interrupted pulmonic blood flow. On a visit to a hospital in Europe, the house staff presented another patient who was flushing, and who had a carcinoid tumor of the liver. It later became apparent that the patient whom he had seen with pulmonic stenosis and flushing also had a carcinoid tumor which had spread to the liver. The classical paper and the description of the patient with a typical ileal carcinoid tumor was conceived, and the disease entered the medical canon.

Almost simultaneously, Lembeck isolated from carcinoid tumors two biologically active substances. One, which he called serotonin, was subsequently chemically identified as 5-hydroxytryptamine.[2] Lembeck stated that he could not reproduce all the symptoms of the syndrome when he gave serotonin to patients with carcinoid tumors. Massive amounts of serotonin produced symptoms, but the patients objected violently and stated that these were not the symptoms that they spontaneously experienced. The second substance has not been identified, but may be the peptide bradykinin. The hallmark of the disease became the excessive production of serotonin and, despite Lembeck's warning, by 1952 all the symptoms of the syndrome were attributed to serotonin. In fact, the current medical writer, William Bennett Bean, wrote a poem summarizing the disease[3]:

This man was addicted to moanin',
Confusion, edema, and groanin',
Intestinal rushes,
Great tri-colored blushes,
And died of too much serotonin.

Thus, the disease was thought to be completely understood and in textbooks the chapters on the carcinoid syndrome have become briefer and briefer. They are likely to become longer in the future, however, for I hope to show this morning that these patients do not "die of too much serotonin," and that the disease has a spectrum of clinical as well as biochemical abnormalities. The arguments that serotonin does not cause all symptoms of carcinoid syndrome are based on the following observations: (1) Serotonin is not produced in excess by all patients who have the carcinoid syndrome; (2) the syndrome changes character depending on the site of the primary carcinoid tumor and not its serotonin production; and (3) the syndrome may be produced by other varieties of tumors, some of which have no ability to increase the production of serotonin.

I shall try to describe the spectrum of the carcinoid syndromes. The ileal carcinoid tumor with a syndrome is the most common. It may be identified at operation and does not produce symptoms (although it probably does produce excess serotonin) until metastasis to the liver occurs. The terminal ileum is the most commonly involved ileal segment. Metastasis occurs first in the mesenteric lymph nodes and then the liver. The huge liver observed in the patient presented this morning is not unusual in a patient with a metastatic carcinoid tumor which has been present for several years. The liver was functioning normally in this patient, as it frequently does, despite massive replacement by neoplastic growth. The left lobe of the liver receives the blood coming from the esophagus, the stomach and the upper small intestine. Tumors in the terminal ileum would be expected to drain into the right lobe of the liver since the venous blood of the ileum drains directly into that lobe. Thus, if

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one finds a patient with an ileal carcinoid tumor and a carcinoid nodule in the left lobe of the liver, the nodule is unlikely to be an isolated metastatic lesion. I think this was the case with the patient today. When patients with carcinoid tumor are operated upon, they frequently have unusually severe fibrotic reactions. These are severe enough to convince experienced surgeons to avoid laparotomy if possible. I think the upper gastrointestinal series in the present case demonstrated the matting and partial obstruction caused by the fibrosis subsequent to laparotomy.

The heart lesions in the classical carcinoid syndrome consist of diffuse deposits of collagen over the entire endocardium including the valve surface.[4] They may interfere with closure to such a degree that very severe insufficiency, stenosis or congestive heart failure occurs. These lesions are usually on the right side of the heart. Serotonin concentration has been presumed to be higher on this side than on the left because lung tissue has abundant monoamine oxidase activity. However, Robertson and his coworkers could not demonstrate consistent significant differences in the serotonin concentration between pulmonary artery and venous blood or a consistent rise in peripheral arterial serotonin during a flush.[5] The predominant lesions will occur on the left side of the heart in patients with hepatic carcinoid tumor when there is an associated atrial septal defect or in patients with bronchial carcinoid tumor, where venous blood from the tumor drains directly into the left atrium. Microscopic lesions of carcinoid heart disease are usually present throughout the endocardium of both sides.

If serotonin were responsible for all the symptoms of carcinoid syndrome, interference with its production or with its effect should abolish or ameliorate the symptoms. N-methylated lysergic acid diamide (methysergide) is a drug which appears to work primarily on the effects of serotonin and does not influence the production of 5-hydroxyindolacetic acid. Administration of this drug produces a predictable decrease in the number and weight of bowel movements. On occasion, when a patient is experiencing malabsorption, the fat content of the stool also decreases.[6] This drug does not, however, consistently alter the flushes or prevent the heart lesions or other symptoms of the carcinoid syndrome. Similarly, if serotonin synthesis is blocked by administration of adequate doses of a decarboxylase inhibitor (alphamethyldopa, for example) the symptoms of the classic syndrome do not change. Serotonin administration may produce a flush when given in huge amounts (3 mg or more), but the flush is usually associated with severe abdominal pain, headache, urinary and fecal incontinence, apnea, a *rise* in the blood pressure and bradycardia.

A retinal lesion, which has not yet been described in the literature, may be seen in the carcinoid patient, but probably is not produced by serotonin. It is found in the patient who consistently flushes. The lesions are very small punched-out areas of postischemic change in the peripheral retina. Usually they do not produce any symptoms, but in one of the patients whom I observed, this lesion was located on the macula and caused blindness during flushing. The peptide bradykinin seems to be able to produce the vascular changes seen in the carcinoid eye lesion.

It has become obvious in the course of observing several patients that the typical carcinoid syndrome which occurs with carcinoid tumors of the ileum is not seen consistently when tumors are located at other sites. In the ileal carcinoid syndrome, at least 99 per cent of the indoles are completely metabolized to 5-hydroxyindolacetic acid (5-HIAA); this is not the case with carcinoid tumors in a particular atypical location. Oates observed an atypical syndrome in a patient with gastric carcinoid.[7] The tumor lacked decarboxylase activity and therefore could not convert 5-hydroxytryptophan (5-HTP) to serotonin (5-hydroxytryptamine). The excessive 5-hydroxytryptophan was secreted into the blood stream and circulated as such until it was decarboxylated by the kidney. In this patient, in addition to 5-HIAA, there was a remarkable increase in the urinary concentrations of 5-HTP and 5-HT. A great deal of histamine was also produced by this patient and it may have been responsible for the unusual, diffuse, "blotchy" flushes and gastric ulcers. A relatively low 5-HIAA, high serotonin and high histamine concentration in the urine are characteristic of patients with primary gastric carcinoid tumor.

Another unusual patient with an atypical carcinoid syndrome was sent to us by an allergy clinic. The patient had a very responsible position with the government. He would frequently go home sick when an exceedingly important deadline was to be met. Between sick spells, he was asymptomatic. During an attack he was admitted to the National Institutes of Health and had a severe flush which did not resemble those we had seen before. In addi-

tion, puffiness of the face, periorbital edema, uncontrollable lacrimation and salivation were prominent features. The flush continued for several days and was associated with hypotension, peripheral edema, tremulousness, fever and oliguria.

Yet another patient came to us with mitral stenosis and similar complaints. She had been operated upon previously for a bronchial carcinoid tumor. When she became oliguric and retained fluid, severe, life-threatening pulmonary edema developed. Between flushes, she had no symptoms. The flushes occurred on a predictable schedule—two days of every nine over a two-year period. Since the patient did have hemodynamically significant mitral stenosis, we wondered if the carcinoid tumor had recurred; indeed it had. Because this patient resembled the previous unusual patient with a bronchial carcinoid tumor, and because there was some evidence that corticosteroids had modified the previous patient's severe flush, we administered prednisone during a flush. No effect was noted. We then gave a large amount of prednisone (40 mg per day) for longer periods and there were no further flushes. Within hours after placebo was substituted for prednisone, three flushes occurred. We resumed prednisone therapy and the patient remained symptom-free for more than two years.[8] During this entire period the patient's excretion of 5-HIAA was only modestly elevated. Steroids in other types of carcinoid syndrome have little effect or may ameliorate the flushing slightly.

The next patient with this variant of the classical syndrome was a piano player in a cabaret. She complained of ceaseless crying but the chief complaint was that she had to take Turkish towels to bed with her to keep her saliva from soaking through the pillow. This story sounded familiar, and we suspected a bronchial carcinoid despite the absence of typical flushes. It was subsequently found that she had a bronchial carcinoid tumor with widespread metastasis.

Interestingly, when we searched the literature we found a very high incidence of pluriglandular adenomatosis, Cushing's disease and acromegaly in the patients with bronchial carcinoid tumors. Typical features of the bronchial carcinoid tumor are summarized in Table 1.

Reports of carcinoid tumor began appearing which stressed the tumor's ability to produce histamine, 5-HTP and catechols. It became apparent that this class of tumors may be multi-potential and capable of producing several biologically

TABLE 1.—*Distinctive Features of the Bronchial Carcinoid Syndrome*

1. Prolonged, severe flushing attacks.
   A. May include:
      Anxiety, tremulousness, disorientation.
      Periorbital and facial edema.
      Excessive lacrimation, salivary gland enlargement with excess salivation, diaphoresis.
      Nausea, vomiting, explosive diarrhea.
      Dyspnea, wheezing.
      Fever.
      Hypotension, tachycardia.
      Oliguria.
      Death during an attack.
   B. Possibility of unique and dramatic control by corticosteroids. Phenothiazine drugs also useful.
2. Widespread metastasis with osteoblastic bone lesions.
3. Left-sided heart lesions, with pulmonary edema during flushing.
4. Association with other endocrine disorders.

active substances. The next question was: Which of the substances produced by the tumor was responsible for the flushes? It could not be serotonin because:

1. Anti-serotonin agents were ineffective in preventing flushes;

2. Serotonin is not made by many tumors associated with the syndrome;

3. Other tumors which produce the carcinoid syndrome may not have the histologic features of carcinoid or the ability to produce serotonin. The latter include pancreatic duct neoplasms, non-beta islet cell adenomas, neoplasms in the biliary tract, stomach and ovaries and oat cell carcinomas of the bronchus;

4. The amount of serotonin excess does not correlate with the severity or frequency of flushes. For example, the patient described today had only a modest elevation in 5-HIAA excretion but very severe symptoms.

We reasoned that if the tissue was able to make many biologically active chemicals, then it could be making another yet undetected chemical responsible for the flush. Moreover, we were impressed that the autonomic nervous system was related to flushes. Patients who experienced nervousness or tension seemed to flush frequently, as did the patient discussed this morning. Was there any relationship between the autonomic nervous system and the production of the flush? Could catechols for some reason have a paradoxical activity and produce flushes and hypotension in carcinoid patients?

As we were thinking thus, so was Robertson, whom I referred to earlier. Dr. Robertson showed

that epinephrine given intravenously to carcinoid patients produced flushes. The flush was associated with profound hypotension just as the patient had experienced in spontaneous flushes. By infusing catechols into the internal carotid artery of a patient with carcinoid tumor, the investigators showed that these flushes were not a direct effect of catechol. The local effect of the epinephrine produced blanching in half of the face, and the systemic effect (flushing) followed in about 60 to 90 seconds. Robertson and later Levine reasoned that catechols were releasing a vasodilating substance responsible for the flush.[9] The same effects were produced by the ingestion of cheese which contained tyramine. Tyramine's major pharmacologic effect is to release endogenous catechols which then indirectly produce the flush.

The relationship between the catecholamine and the flush has practical importance. As was illustrated this morning, subpharmacologic doses of catechols can be used as a diagnostic test in evaluating the carcinoid patient who has low 5-HIAA excretion. In addition, one must remember that agents which increase peripheral vascular resistance by the release of endogenous catechols cannot be used during operation because they will continue to provoke the flush and the hypotension associated with it. Such agents include epinephrine, norepinephrine, metaraminol and mephentermine. When a drug must be used to increase peripheral vascular resistance, it has to be one which has a direct effect on the small vessels independent of catechol release, for example, methoxamine or angiotensin. The latter two drugs can increase blood pressure without provoking a flush.

If catechols do not produce the flush, what does? We looked for a substance which could lower blood pressure, stimulate lacrimation and salivation, produce edema, increase cardiac output and be released by catecholamines. Among vasodilator peptides which are normally found in the gut, in the central nervous system and in the lacrimal and salivary glands is bradykinin. Intravenous administration of bradykinin produced a flush which was similar to the spontaneous and epinephrine-provoked flushes.[10] In addition, the peripheral vascular changes associated with a spontaneous flush were mimicked by the administration of bradykinin. Finally, we were able to look for the enzyme kallikrein, which produces bradykinin and the peptides themselves in several patients with the carcinoid syndrome. Our data are summarized by the following statements:

1. Kallikrein can be found in some carcinoid tumors. Dr. Nathan Back of Ohio has detected kallikrein in the primary tumor of the patient presented today;

2. This kallikrein is released into the systemic circulation during a flush;

3. The peptide itself can be isolated from the hepatic vein during an epinephrine-induced flush;

4. The peptide formed by the tumor kallikrein has been characterized and it is lysyl-bradykinin.[11]

Oates has identified bradykinin in hepatic venous blood.[12] The kinin concentration rises in the blood in association with the flushes, the drop in mean blood pressure and an increase in forearm blood flow.[13] (Chart 1.) These facts, I think, relate the kallikrein-kinin system as a pathogenetic one in the production of the flush (Chart 2).

We do not have time to discuss treatment, but one can treat symptomatically if one knows what the tumor is producing. There is no good evidence that antitumor agents are effective in decreasing symptoms or in changing the prognosis in this disease. These agents need further, controlled evaluation.

In summary, we must now view the carcinoid syndrome as a series of events which can be pro-

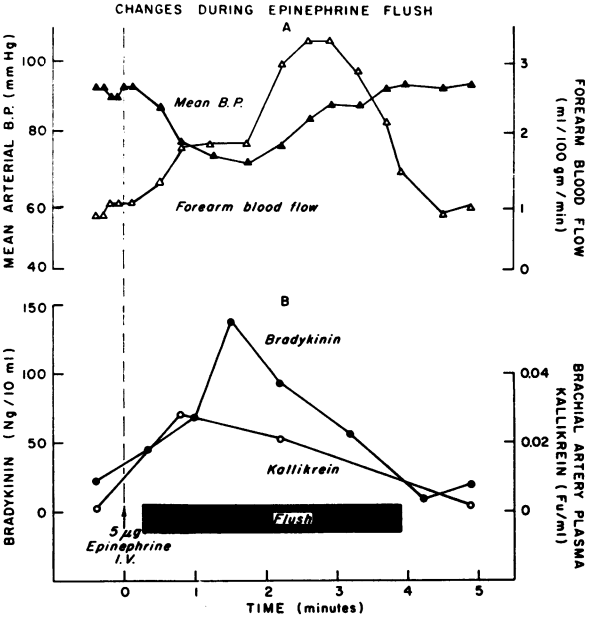

Chart 1.—Serial determination of mean arterial pressure (B.P., solid triangles), forearm blood flow (open triangle, top panel A), bradykinin (closed circles), and kallikrein (open circles, bottom panel B) before and after intravenous injection of epinephrine into a patient with carcinoid tumor. The lower than normal control values for forearm blood flow are compatible with the fact that the patient was in congestive heart failure.[13] Fu=Frey Unit; Ng=Nanogram (also called millimicrogram).

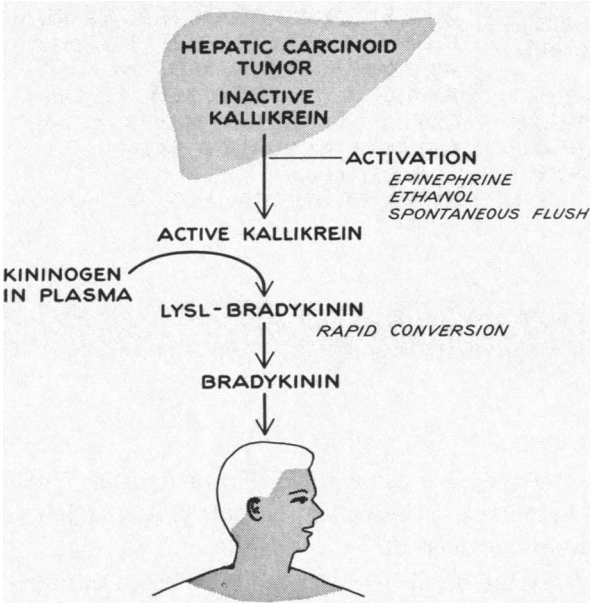

Chart 2.—Summary of the present concepts by which kallikrein and kinins may contribute to the carcinoid flush. The flush mechanism, however, is complex; in some patients, kinin levels are normal. (Chart reprinted by permission of *Physiology and Pharmacology for Physicians*, "Kinins in Medicine—Present and Future," Melmon, K. L., Vol. 1, No. 6, June 1966, p. 3.)

duced by a variety of tumors, including neoplasms that have no relationship to carcinoid tumor. When the tumor has the histological characteristics of carcinoid, the syndrome produced seems dependent upon the location of the primary growth. Any tumor may produce a variety of biologically active chemicals at any given time. These chemicals include serotonin, 5-hydroxytryptophan, histamine, catecholamines and vasodilator peptides-kinins. It may be possible that the tumors are capable of producing other vasoactive peptides or even more sophisticated proteins capable of inducing such changes as acromegaly, pluriglandular adenomatosis, Cushing's disease or pigmentation. It seems reasonable to view the syndrome in a particular patient as the momentary "algebraic sum" of these biologically active substances. It also appears mandatory to evaluate each case separately and thoroughly before reasonable therapy is offered or can be expected to be efficacious.

DR. LLOYD H. SMITH, JR.*[3]: I think the applause reflects the outstanding job that Dr. Melmon has done pulling together this clinical syndrome and its background and the chemical and pharmacologic features.

Recent Summaries in the Literature

1. Thorson, A., Biörck, G., Björkman, G., and Waldenström, J.: Malignant carcinoid of the small intestine with metastasis to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. A clinical and pathologic syndrome, Am. Heart J., 47:795, 1954.

2. Lembeck, F.: 5-hydroxytryptamine in a carcinoid tumor, Nature, 172:910, 1953.

3. Bean, William B.: Vascular Spiders and Related Lesions of the Skin, Charles C Thomas, 1958, p. 117.

4. Roberts, W. C., and Sjoerdsma, A.: The cardiac disease associated with the carcinoid syndrome (carcinoid heart disease), Amer. J. Med., 36:5, 1964.

5. Robertson, J. I. S., Peart, W. S., and Andrews, T. M.: The mechanism of facial flushes in the carcinoid syndrome, Quart. J. Med., 31:103, 1962.

6. Melmon, K. L., Sjoerdsma, A., Oates, J. A., and Laster, L.: Treatment of malabsorption and diarrhea of the carcinoid syndrome with methysergide, Gastroenterology, 48:18, 1965.

7. Oates, J. A., and Sjoerdsma, A.: A unique syndrome associated with secretion of 5-hydroxytryptophan by metastatic gastric carcinoids, Amer. J. Med., 32:333, 1962.

8. Sjoerdsma, A., and Melmon, K. L.: Severe flushing reactions responsive to steroids in patients with bronchial carcinoid, Lancet, 2:791, 1964.

9. Levine, R. J., and Sjoerdsma, A.: Pressor amines and the carcinoid flush, Ann. It. Med., 58:818, 1963.

10. Oates, J. A., Melmon, K. L., Sjoerdsma, A., Gillespie, L., and Mason, D.: Release of a kinin peptide in the carcinoid syndrome, Lancet, 1:514, 1964.

11. Melmon, K. L., Lovenberg, W., and Sjoerdsma, A.: Identification of lysylbradykinin as the peptide formed in vitro by carcinoid tumor kallikrein, Clin. Chim. Acta, 12:292, 1965.

12. Oates, J. A., Pettinger, W. A., and Doctor, R. B.: Evidence for the release of bradykinin in carcinoid syndrome, J. Clin. Invest., 45:173, 1966.

13. Mason, D. T., and Melmon, K. L.: Abnormal forearm vascular responses in the carcinoid syndrome: The role of kinins and kinin generating systems, J. Clin. Invest., 48:1685, November 1966.

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